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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,391	MARTH ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9-7-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 9-7-04.

Claims 36-49 are pending in instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 36-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of systemic C2 GlcNAc T^{Δ} or conditional C2 GlcNAc T^{F} homozygous mice using Cre-lox P recombination, whereby a deficiency of C2 GlcNAc transferase activity and a deficiency of core 2 O-glycan synthesis were observed in isolated null mouse splenocytes, does not reasonably provide enablement for methods of inhibiting inflammatory responses in a mammal, or for methods of modulating binding of a first myeloid cell to a second myeloid cell or to an endothelial cell in an organism comprising the administration of a compound that modulates the synthesis of a core 2 oligosaccharide or the administration of a compound that inhibits the activity of a core 2 GlcNAc transferase in an organism for the same reasons of record as set forth in the Office action mailed 6-2-04.

Applicants argue that the examiner has provided nothing to show that one of skill would doubt that a wide range of inhibitors would be useful in the claimed methods.

Applicants also argue that Appellant need not provide working examples using all inhibitors useful in the claimed methods. Contrary to Applicants' assertions, the examiner has provided appropriate and adequate reasoning, in view of the state of the art at the time of filing, and in view of the record before us for the instant case, to illustrate that the ability to provide the treatment effects claimed in a mammal would require undue experimentation beyond that provided. The claims are drawn to methods of inhibiting any inflammatory response, acute or chronic inflammatory disease or condition in a mammal, and methods of inhibiting binding of a first myeloid cell to an endothelial cell or to a second myeloid cell in a mammal, comprising the administration (by any route) of any compound that inhibits core 2 GlcNAc transferase activity.

The specification teaches a deficiency in C2 GlcNAc transferase activity and in core 2 O-glycan synthesis in isolated splenocytes obtained from null mice (i.e. C2 GlcNAc T^{Δ} or conditional C2 GlcNAc T^{F} homozygous mice). The specification and the art are silent regarding the administration, by any route, of any inhibitors of core 2 GlcNAc transferase, whereby any acute or chronic inflammatory disease or condition is inhibited in a mammal. The specification and art are also silent regarding the administration, by any route, of any of the various inhibitors of core 2 GlcNAc transferase claimed, whereby binding of a first myeloid cell to an endothelial cell or to a second myeloid cell is inhibited in a mammal.

The cellular and biochemical phenotypes observed in cells/tissues removed from C2 GlcNAc T null mice, for instance, that display a deficiency in P and E selectin ligands, are not representative of the ability to achieve these phenotypes in vivo

following administration of C2 GlcNAc T inhibitors. The latter ability requires undue experimentation beyond that provided in the instant specification - to achieve the level of inhibition of C2 GlcNAc T obtained in null mutants by administering enzyme inhibitors. The observed phenotypes associated with the generation of gene knockouts or null mutants are not representative of the ability to appropriately and effectively administer any of the inhibitors claimed, including sugar nucleotides and acceptor substrate analogs of core 2 GlcNAc transferase, whereby treatment effects are provided or cellular binding is inhibited in a mammal.

Applicants argue that the references of Hindsgaul and Jain are inappropriate in illustrating unpredictability in the art, and that they instead support the position held by Applicant that the art of making and testing glycosyltransferase inhibitors was advanced at the time of the invention. Applicants are correct that the in vitro testing of inhibitors of glycosyltransferases has been and is being actively investigated and advanced in the field of glycobiology. Hindsgaul and Jain, however, are reasonably relied upon to illustrate that even on an in vitro level, candidate inhibitors of glycosyltransferases must be empirically tested for their inhibitory capabilities because molecules thought to theoretically function as effective inhibitors fail to do so (*see* Hindsgaul et al, J. Biol. Chem., 266(27), at page 17,861, first full paragraph: "The results of the inhibition studies presented in Table I could not have been anticipated.").

Applicants argue that Jain is inappropriately relied upon because it does not relate to inhibitors useful in the present invention. That is, it does not describe compounds that act as acceptor analogs of C2 GlcNAcT. Applicant is correct that the

reference deals with sialyl structures that are distal on the glycan, and therefore does not literally deal with inhibitors involving the earlier actions of C2 GlcNAcT. But, contrary to Applicants' assertions regarding the general relevance of this reference, Jain illustrates that, even though modeling studies predict the structural similarities of potential ligands for glycosyl transferases, until they are empirically tested, it cannot be assumed that they will function in a predictable manner: "It is not clear at this time why an oligosaccharide containing GalNAc-beta1-4(Fuc alpha-1-3)GlcNAc-beta-1-OMe sequence... appears to be a better ligand for E-selectin." (*see* Jain, Glycobiology, 8(7), at page 712, first full paragraph).

In addition, and contrary to Applicants' assertions, it is highly unpredictable to extrapolate from in vitro success, once achieved, to in vivo efficacy. Lowe makes clear the unpredictability of in vivo treatments for inflammation using the instantly claimed approach (J. Clin. Invest., 99(5), page 823, bridging paragraph between left and right columns, document "AI" in the IDS filed 9-7-04): "Antibody blocking studies have been informative because these reagents bind with high affinity to their cognate antigens... by contrast, the other types of inhibitory molecules are generally smaller, have intravascular half lives that are much shorter, or less well-defined, and may have lower affinities and/or specificities for the cognate receptor. Most interventional efforts have made use of acute inflammatory models that assess neutrophil recruitment, due to the lack of long-acting selectin blocking reagents, difficulties arranging continuous, long-term intravascular delivery of the available short acting inhibitors, and the paucity of information concerning the functional relevance of selectin-dependent leukocyte

recruitment in chronic inflammatory conditions." The examples provided in the instant specification, of the deficiency of C2 GlcNAc transferase activity and of core 2 O-glycan synthesis in cells obtained from C2 GlcNAc T null mice, do not address these variables listed by Lowe, and which variables are associated with adequately targeting and delivering the claimed inhibitors to appropriate target cells and tissues, whereby cellular binding or treatment effects are provided in a mammal.

And in further addressing the unpredictability of in vivo efficacy in this field, Lowe states the following: "There is a need for a more detailed exploration of the in vivo consequences of selectin ligand antagonism to the complex signal transduction processes associated with selectin-dependent cell adhesion. ...There is also a need to better understand the functional relevance of circulating, soluble forms of selectins and some of their counter-receptors, especially since the levels of these molecules can fluctuate in concert with inflammatory conditions, and may, at least in principle, regulate selectin-dependent adhesion and signal transduction processes in vivo. ...Mice with genetic deficiencies in the selectins, or their counter-receptors, should prove useful for this work, **although caution in interpreting data from such mice needs to be exercised**." (*Id.,* page 825, last paragraph, emphasis added).

Applicants also assert that identification of non-exemplified inhibitors is entirely routine in light of the state of the art and standard assays known at the time of the invention. Contrary to Applicants' assertions the identification of effective enzymatic inhibitors using non-exemplified candidates is highly unpredictable in the art, and this conclusion is reasonably supported by i) the teachings of Hindsgaul and Jain regarding

the unpredictability of modeling studies to accurately identify inhibitors that are effective in vitro; ii) in light of the teachings of Lowe regarding the inability to extrapolate from in vitro to in vivo situations because of such highly unpredictable variables as sustaining adequate delivery of inhibitors at appropriate target sites in vivo; iii) in light of the complications arising from the presence of soluble forms of selectins or counter receptors; and iv) due to the inability to extrapolate from genetically deficient mice to achieving efficacy upon the in vivo administration of inhibitors. For these reasons, the instant invention remains rejected for lacking enablement over the scope claimed.

Related Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Nakamura et al (J. Biol. Chem., 273(41) : 26,779-26,789 (1998)) teach decreased expression of core 2 mRNA transcript in KM3 cells following TPA treatment, in turn reflecting a decrease in enzyme expression/enzyme activity levels (see abstract on p. 26,779, last paragraph of the introduction on p. 26,780, figure 6 on p. 26,786, bridging paragraph pages 26,786-26,787). Nakamura is distinguishable from the instant invention because Nakamura et al teach decreased core expression, not enzyme activity, upon induction of cellular differentiation using TPA.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JZ
11-4-04

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